## Remarks

Claims 1, 2, 4-19, 23-33 and 44-48 are pending. By this amendment and response, claims 1, 2, 44, 47, and 48 are amended, and claims 3 and 20-22 are canceled without prejudice or disclaimer. No new matter is added.

## Claim Objections

Claim 46 was objected to for lacking a period at the end of the claim. Applicant has amended the claim to include the period.

## Rejection Under 35 U.S.C. § 112, first paragraph

Claims 47 and 48 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

***The Legal Standard for Enablement***

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d 1361, 1365, 42 USPQ2d 1001, 1004 (quoting *In re Wright* , 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir.

1993). See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. See *Ex parte Jackson*, 217 USPQ 804, 807 (PTO Bd. App. 1982). There is no requirement for examples.

***Analysis***

Claim 47 is amended to include the elements of originally filed claim 48 and to clarify that the method assists in the diagnosis of cancer by detecting an oncogene or variant thereof known to be involved in or related to cancer or a predisposition to cancer. Basis for the amendment is found, for example in the paragraph bridging pages 11 and 12, and page 23, lines 18-20. No new matter is added. Claim 47 is further amended to clarify that the second primer comprises a region for hybridizing to the first primer that consists of one to three types of nucleotides selected from the group consisting of A, T or U, G, and C. Basis for this amendment is found, for example at page 9, lines 10-29 and Figure 3. Claim 48 is amended to clarify that the target polynucleotide encodes a protein selected from the group consisting of growth factors, receptor tyrosine kinases, membrane associated non-receptor tyrosine kinases, G-protein coupled receptors, membrane associated G-proteins, serine/threonine kinases, and nuclear DNA-binding/transcription factors. Basis for this amendment is found for example at page 12, lines 7-10.

*The Specification Provides Detailed Guidance for Methods for Assisting in the Diagnosis or Detection of Cancer*

One of skill in the art would not engage in undue experimentation to practice the claimed method for assisting in the diagnosis or detection of cancer based on the guidance provided in the specification alone or in combination with the knowledge available at the time the application was filed. For example, the specification lists several representative categories of oncogenes on page 12, lines 7-10 including growth factors, receptor tyrosine kinases, membrane associated non-receptor tyrosine kinases, G-protein coupled receptors, membrane associated G-proteins, serine/threonine kinases, and nuclear DNA-binding/transcription factors. Specific oncogenes in each of these categories are disclosed on page 12, line 11 to page 13, line 20. Nucleic acid sequences for the disclosed genes are known in the art and available from databases such as Genbank.

*The Specification Provides Working Examples*

Although not necessary, the specification also contains working examples of the claimed method. Example 3 describes detecting the presence or absence of known oncogenes p53 and raf in cancer tissue. The specification further teaches that the presence, absence, or amount of detectable oncogene can be used to assess the risk of developing a pathology (p. 23, lines 19-20).

*The Detection of Nucleic Acids or Variants Thereof for Assisting in the Diagnosis of Cancer Was Known in the Art*

The presence of certain oncogenes or variants thereof is known in the art to be indicative of a predisposition to cancer. Applicant encloses a copy of Eeles, Rosalind (2000) Breast Cancer

Research, 2(4):283-290 which expressly provides that mutations in *BRCA1* and *BRCA2* predispose a female patient to breast cancer. Both genes also confer an increased risk for prostate cancer (p. 283). Frame et al. (1998) Phi. Trans. R. Soc. Lond. B, 33:839-845 discloses that the concept that genes predispose individuals to develop cancer has been confirmed by the isolation and identification of a large and increasing number of genes that can be passed through the germline in mutant form (p. 840, copy enclosed).

Additionally, numerous U.S. patents have issued for the detection or diagnosis of cancer by detecting the presence of specific nucleic acids or polypeptides they encode. For example U.S. Patent No. 5,989,815 having an issue date of November 23, 1999, claims a method for detecting genetic mutations associated with a predisposition with cancer. U.S. Patent No. 5,866,323 having an issue date of February 2, 1999, claims a method for assisting in the diagnosis of cancer by detecting specific nucleic acids. Numerous post-filing U.S. patents for the diagnosis of cancer have also issued including U.S. Patent No. 7,078,180; 6,998,232, 6,939,675; 6,300,059; and 6,245,501. Thus, methods for diagnosing cancer or assisting in the diagnosis of cancer by detecting specific nucleic acids were known and enabled in the art.

In view of the detailed guidance in the specification, the presence of working examples, and the knowledge available at the time the application was filed, Applicant submits that the specification is enabling and the rejection should be withdrawn.

## Rejection Under 35 U.S.C. § 112, second paragraph

Claims 6, 9-11, and 24 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

Claim 6 is rejected because the term "high stringency" is allegedly unclear. The term "high stringency" is an art recognized term. Moreover, the specification includes a definition of the term on page 18, lines 17-21. It is well known that an Applicant can be his own lexicographer. See MPEP § 2111.01, page 2100-50. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

Claims 9-11 are amended to address matters of form, and the rejection is overcome.

Claim 24 is rejected because it is allegedly unclear whether the second primer is attached to a solid support. Applicant respectfully submits that one of skill in the art would understand that the second primer contains a moiety that enables the second primer to be bound to a solid support. The claim does not require that the second primer be bound to a solid support, and the claim is not vague.

## Rejection Under 35 U.S.C. § 102

Claims 1-33, 47 and 48 were rejected under 35 U.S.C. § 102(b) as being anticipated by Koster et al. (US 2002/0042112). Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

***Legal Standard***

To anticipate a claim for a patent, a single prior source must contain all of the claimed elements. Federal Circuit decisions repeatedly emphasize that anticipation is established only if the following three standards are met: (1) all the elements of an invention, as stated in a patent claim, (2) are identically set forth, (3) in a single prior art reference. *See e.g. Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 62 USPQ2d 1865 (Fed. Cir. 2002); *EMI Group North America, Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350, 60 U.S.P.Q.2d 1423 (Fed. Cir. 2001).

***Analysis***

Claim 1 is amended to clarify that the first primer is extended using one to three of four types of non-terminator nucleotides selected from A, T or U, G, and C to produce equal length primer extension products, and the extended portion of the first primer comprises one to three of four types of nucleotide. Claim 1 is further amended to clarify that the second primer comprises a region complementary to the extended portion of the first primer consisting of one to three of four types of nucleotides. Basis for the amendment is found in the specification as filed, for example page 9, lines 10-19 and Figure 3. Claim 2 is amended to clarify that the extended portion of the first primer consists of one to three of the four types of nucleotides. Claim 3 is canceled without prejudice or disclaimer. Claims 47 and 48 are amended as discussed above.

The methods of independent claims 1 and 47 require two single primer extension reactions to be performed. The first primer extension reaction requires equal length primer

extension products to be produced. In claim 1, the first primer extension product is formed using one to three of four types of nucleotides selected from the group consisting of A, T or U, G, and C, and this extended sequence only contains one to three of four types of nucleotides and serves as the template for the second primer extension reaction. The sequence of the second primer complementary to the extended portion of first primer consists of one to three of four types of nucleotides selected from the group consisting of A, T or U, G, and C nucleotides.

Claim 47 requires that the non-terminator nucleotide mixture be formulated to produce equal length extension products and that the sequence of the second primer complementary to the extended portion of first primer consists of one to three of the four types of nucleotides.

Koster et al. fails to disclose the methods of claim 1 or claim 47 for at least the reason that Koster et al. fails to disclose using one to three of the four types of nucleotides to obtain equal length extension products in the first primer extension reaction. Indeed, if Koster et al. were to use three of the four types of nucleotides in the first primer extension reaction, the target nucleic acid would not be amplified as required because the extension reaction would terminate whenever the polymerase reached a nucleotide for which the complement was omitted (see paragraphs 395-408).

Koster et al. is also distinguishable from the claimed methods because Koster et al. uses terminator nucleotides in the second primer extension reaction to obtain detectable primer extension products having lengths corresponding to the type of mutation to be detected. In the claimed methods, the second primer extension reaction is not performed in the presence of

terminator nucleotides because the longer the second extension product, the more labeled nucleotides will be incorporated thereby creating a stronger single for detection.

Moreover, Koster fails to disclose that the extension portion of the first primer is composed of only one to three types of nucleotides, and that the region of the second primer complementary to the first primer is composed of one to three types of nucleotides. Thus, Koster et al. fails to anticipate claims 1 and 47.

Because dependent claims incorporate the elements of the claims from which they depend, dependent claims 2-33 and 48 are not anticipated for at least the reason independent claims 1 and 47 are not anticipated.

*Koster et al. Does not Inherently Disclose Formation of Equal Length Extension Products with One to Three of Four Types of Nucleotides*

The Examiner contends that PCR inherently produces equal length extension products and because Koster et al. discloses using PCR, Koster et al. inherently disclose producing equal length extension products. This conclusion is factually incorrect. Applicants enclose a copy of Olsen et al. *Incomplete primer extension during in vitro DNA amplification catalyzed by Taq polymerase; exploitation for DNA sequencing,* Nucleic Acids Research, 17(23):9613-9620 (1989) in which the authors report that PCR reactions using *Taq* polymerase produce multiple fragments which are shorter than the full length product (p. 9613). Figure 3 shows a polyacrylamide gel analysis of PCR fragments produced over multiple rounds of PCR. Thus, it was known in the art that PCR amplification does not produce equal length extensions products. Because Koster et al. does not inherently disclose the production of equal length extension

products, Koster et al. cannot anticipate the claims. Moreover, the PCR reaction can not be performed with one to three type nucleotides.

**Rejection Under 35 U.S.C. § 103**

Claims 44-46 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Koster et al. (US 2002/0042112), in view of Wang (EP 1 162 278 A2). Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

***The Legal Standard for Obviousness***

References relied upon to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., "they must place the claimed invention in the possession of the public." *Application of Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245 (C.C.P.A. 1979); *see Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 U.S.P.Q.2d 1301 (Fed. Cir. 1989). A publication that is insufficient as a matter of law to constitute an enabling reference may still be relied upon, but only for what it discloses. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed. Cir. 1984); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991).

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose

among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *See In re Geiger* , 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

Obviousness is determined as follows. "A proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *Noelle v. Lederman*, 355 F.3d 1343, 69 USPQ2d 1508 (Fed. Cir. 2004). Both a suggestion to make a claimed composition or process and a reasonable expectation of success must be founded in the

prior art, not in the applicant's disclosure. *Velander v. Garner*, 348 F.3d 1359, 68 USPQ2d 1769 (Fed. Cir. 2003)*; see also In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

***Analysis***

As noted above, Koster et al. fails to disclose or suggest a method for detecting a target polynucleotide in which a first primer isometric extension product serves as the template for a second primer extension reaction and wherein the second primer extension product has a region complementary to the first primer extension product wherein the region consists of the one to three types of nucleotides selected from the group consisting of A, T or U, G, and C. Contrary to the assertions of the Examiner, Koster et al. does not explicitly or inherently disclose the formation of equal length primer extension products (see discussion above). Moreover, the PCR extension reactions taught by Koster et al. utilize a set of primers for each extension reaction (see paragraph 395). Each primer flanks the sequence to be amplified. Koster et al. essentially describes amplifying a target nucleic acid, affinity capturing the amplified target nucleic acids, and performing a primer extension reaction by hybridizing a detection primer to the amplified target nucleic acid and using ddNTPs to have a definitive termination site (paragraphs 388 to 408).

Claim 44 requires forming equal length primer extension products using a nucleotides consisting of X, Y, and Z, wherein X and Y are different purine non-terminator nucleotides, and Z is a pyrimidine non-terminator nucleotide; or X and Y are different pyrimidine non-terminator nucleotides, and Z is a purine non-terminator nucleotide. Claim 44 is amended to clarify that the

second primer comprises a region for hybridizing to the first primer consisting of one to three types of nucleotides selected from the group consisting of A, T or U, G, and C. Basis for this amendment is found in the specification as filed, for example at page p. 9, lines 10-19 and Figure 3. Neither Koster et al. nor Wang disclose or suggest a method using such a second primer. Indeed, the second primer (detection primer) used by Koster et al. binds to the interior region of the first primer extension product (See Figure 34A and 34B).

Koster et al. also fails to disclose or suggest producing extension reaction products using three of the four types of nucleotides. Accordingly, Koster et al. fails to disclose or suggest each of the elements of the claims.

*The Combination of Koster et al. and Wang Fails to Disclose or Suggest Each Element of the Claims*

Wang fails to cure the deficiency of Koster et al. Specifically, Wang fails to disclose or suggest a second primer extension reaction using a second primer having a region complementary to the first primer consisting of one to three types of nucleotides selected from the group consisting of A, T or U, G, and C. Additionally, unlike the method of Wang, the claimed method has a second primer extension reaction that does not require the omission of one of the four types of nucleotides or the presence of a terminator nucleotide. Thus, the combination of references fails to disclose or suggest every element of the claims, and the combination cannot render the claims obvious.

*The Modification of Koster et al. with Wang Renders the Method of Koster et al Inoperable*

The first primer extension reaction of Koster et al. is the PCR amplification of the target nucleic acid which requires the presence of all four types of nucleotides. Wang et al. teach the production of isometric extension products by omitting one of the four types of nucleotides from a single primer amplification reaction. The omission of one of the four types of nucleotides from the PCR amplification step of Koster et al. would prevent the full length target nucleic acid from being amplified. Thus, the target nucleic acid containing the putative mutation would not be produced and therefore could not be detected. If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Because the modification of Koster et al. with Wang would render the method of Koster et al. inoperable, there can be no motivation to combine the references.

*Koster et al. Teaches Away from the Claimed Methods*

The first primer extension reaction of Koster et al. discloses that all four nucleotides are required to amplify the target nucleic acid (paragraphs 327, 344, and 395-408). The claimed methods require the omission of at least one of the four types of nucleotides to produce equal length primer extension products from the first primer. Because Koster et al. teaches that all four nucleotides must be present in the first primer extension reaction, Koster et al. teaches away from the claimed methods. One of ordinary skill in the art would not be motivated to combine the references in view of Koster et al.'s specific teaching that all four nucleotides are required in

the first primer extension reaction. Thus, the references do not render the claimed methods obvious.

## Amendments to the Specification

Applicant has amended the specification to clarify that the disclosed methods include nucleotide mixtures containing two purine nucleotides and one pyrimidine nucleotide or two pyrimidine nucleotides and one purine nucleotide. Basis for the amendment is found for example in the paragraph bridging pages 2 and 3. No new matter is introduced.

## Conclusion

Allowance of claims 1, 2, 4-19, 23-33 and 44-48 is respectfully solicited. However, in the event that the Examiner is inclined to reject any of the claims in this application, Applicants respectfully request an interview with the Examiner prior to the issuance of a further Office Action.

Respectfully submitted,

/Charles Vorndran/
Charles Vorndran
Reg. No. 45,315

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PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)